Indoor Coal Combustion Emissions, *GSTM1* and *GSTT1* Genotypes, and Lung Cancer Risk: A Case-Control Study in Xuan Wei, China[1]

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Abstract

The lung cancer mortality rate in Xuan Wei County, China is among the highest in the country and has been associated with exposure to indoor smoky coal emissions that contain high levels of polycyclic aromatic hydrocarbons. This risk may be modified by variation in metabolism genes, including *GSTM1*, which encodes an enzyme known to detoxify polycyclic aromatic hydrocarbons. To investigate the relationship between *GST* genotypes and lung cancer risk in Xuan Wei County, we analyzed *GSTM1* and *GSTT1* genotypes in a population-based case-control study. A total of 122 lung cancer patients and 122 controls, individually matched by age, sex, and home fuel type, were studied. Compared to subjects who used less than 130 tons of smoky coal during their lifetime, heavier users (≥130 tons) had a 2.4-fold (95% confidence interval, 1.3–4.4) increased risk of lung cancer. The *GSTM1*-null genotype was associated with a 2.3-fold (95% confidence interval, 1.3–4.2) increased risk of lung cancer. Furthermore, there was some evidence that smoky coal use was more strongly associated with lung cancer risk among *GSTM1*-null versus *GSTM1*-positive individuals. In contrast, the *GSTT1* genotype was not significantly associated with lung cancer risk. Our data suggest that the *GSTM1*-null genotype may enhance susceptibility to air pollution from indoor coal combustion emissions.

Introduction

In rural Xuan Wei County, Yunnan Province, China, the lung cancer mortality rate is five times the national average. Females in Xuan Wei County are almost all nonsmokers, yet they have the highest lung cancer rate in China (eight times the Chinese national average for females), and the rate among men is also among the highest in China. In general, male lung cancer mortality rates are usually higher than female rates, presumably because of their higher smoking rates. It is very unusual to find similar female and male lung cancer mortality rates (especially when the females are mostly nonsmokers), but this is the case in Xuan Wei (27.7 and 25.3 per 100,000 for males and females, respectively; Ref. 1).

Previous studies have shown an etiological link between lung cancer mortality and domestic smoky coal use. Smoky coal emissions contain high concentrations of PAHs[3] (1–5). Indoor air concentration of particulate matter and extractable organic matter can reach as high as 24.4 and 17.6 mg/m^3, respectively, during the burning of smoky coal for home cooking and heating (1). The corresponding concentrations of benzo(*a*)pyrene, an indicator of PAHs, can become as high as 14.7 μg/m^3 (6) during cooking, comparable to exposure levels experienced by coke oven workers.

The role of genetic polymorphisms in relation to lung cancer risk has not been investigated previously in Xuan Wei. The polymorphic GST superfamily encodes enzymes that are known to catalyze the conjugation of xenobiotics and glutathione, and thus, these genes may play a significant role in the detoxification and occasional activation of xenobiotics. Normal or increased GST enzyme activity may protect susceptible tissues from somatic mutations in cellular DNA by facilitating the conjugation and subsequent elimination of electrophilic carcinogens. Carriers of homozygous deletions in the *GSTM1* and *GSTT1* genes display a lack of GSTM1 and GSTT1 enzyme activity, respectively (7). The GSTM1 enzyme detoxifies the reactive metabolites of PAHs and other electrophilic carcinogens, whereas the GSTT1 enzyme metabolizes other potential carcinogens, such as halomethanes and ethylene oxide (8, 9). Variant forms of these susceptibility genes are common in the population, and based on their specific substrate specificities, they may interact only with particular components of an environmental exposures and thereby alter risk of developing lung cancer. Given that lung cancer risk in Xuan Wei County is in great part attributable to exposure to high levels of indoor air pollutants, including PAHs, we carried out a case-control study to determine whether the *GSTM1* or *GSTT1* genotype was associated with increased lung cancer risk.

Received 5/3/99; revised 3/22/00; accepted 4/1//00.

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[1] The research described here has been reviewed by the National Environmental and Health Effects Research Laboratory of the United States Environmental Protection Agency and approved for publication.

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[3] The abbreviations used are: PAH, polycyclic aromatic hydrocarbon; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GST, glutathione *S*-transferase; OR, odds ratio.

Subjects and Methods

Study Design and Inclusion Criteria. This was a population-based case-control study. All residents of Xuan Wei were considered the target population. During the period from March 1995 to March 1996, 135 newly diagnosed lung cancer cases, based on a minimum of clinical symptoms and X-ray, were identified at Xuan Wei County Hospital, Yang Chang Mine Hospital, Lai Bin Mine Hospital, Yun Dan Hospital, and the Yunnan Provincial First People's Hospital (located in Kunming). Almost all lung cancer cases diagnosed in Xuan Wei County are admitted to one of these five hospitals. Among the 135 cases, 133 cases (98%) agreed to participate in this study. The additional criteria for inclusion as a lung cancer case for this study were as follows: (*a*) confirmation of the clinical diagnosis of lung cancer based on the examination of tissue (14 cases; 10.5%), tracheal lavage and tracheal brushing (21 cases; 15.8%), or sputum sample (70 cases; 52.6%); or (*b*) the subject died within a 1-year period (17 cases; 12.8%). We chose the 1-year limit based on a report by Hu *et al.* (10) showing that the 1-year survival rate among Xuan Wei lung cancer patients was 43.2%. Thus, we used death within 1 year as a way to substantiate the diagnosis of lung cancer for those for whom we had only clinical symptoms and X-ray records available. A total of 122 lung cancer cases met the above inclusion criteria. Among them, cell type information on 35 cases was available including 24 non-small cell carcinoma, 3 small cell carcinoma, and 8 others.

One control was selected for each lung cancer case, matching by sex, age (±2 years), village, and type of fuel currently used for cooking and heating at home. Within 2 weeks after the diagnosis and recruitment of each lung cancer case, a control was selected randomly from the list of household registrations (which included age and sex) from the same villages in which the lung cancer patient lived. The participation rate of the controls was 100%. A standardized closed-question form of questionnaire was used to obtain demographic information, smoking history, family and personal medical history, and information on other variables. Each subject was asked to recall the total tonnage of smoky coal or the number of tractor loads (which can be equated with tonnage) that were purchased annually from the local coal distributor. The subjects were also asked about any change in the rate of their consumption of smoky coal. The cumulative exposure to smoky coal use for a given individual was determined by multiplying the annual rate of smoky coal use times the number of years. Coal consumption was generally fixed for the households over the life cycle of the family. Trained investigators interviewed all cases at the hospital, whereas controls were interviewed in their homes. For the protection of the human subjects, this international research study was conducted according to the guidelines of the World Medical Association Declaration of Helsinki. All of the subjects in this study signed a consent form. The research protocol was approved by an EPA Human Subjects Research Review Official.

Buccal Cell Sample Collection. Each case and control provided a sample of buccal cells for genotyping. They used a toothbrush to loosen the buccal cells and then rinsed with a saline solution. The buccal cells were attached to the toothbrush and then washed into the saline solution; these were collected and stored in a second saline solution containing 50% ethanol at –20°C. The buccal cells were transported to the United States by air and immediately frozen at –20°C.

Genotyping. DNA was isolated from the buccal cells as described previously (11). Determination of *GSTM1* and *GSTT1* genotypes was conducted using a previously reported PCR-based method (12, 13). This method included using both *GST*-specific primer pairs and a third primer pair for β-globin in the same amplification mixture. The absence of either a *GSTM1*- or a *GSTT1*-specific fragment indicated the corresponding null genotype. A β-globin-specific fragment was used as a positive control for the adequacy of PCR. The buccal cell sample from each subject was assayed twice. Evaluation of genotypes was carried out blinded to case status.

Statistical Methods. Matched ORs and 95% CIs were used to estimate the association between lung cancer and *GST* genotypes and other risk factors by univariate and multiple conditional logistic regression using Statistical Analysis Software, version 6.12 (SAS Institute Inc.), and S-PLUS for Windows (MathSoft Inc., Cambridge, MA). The OR for smoky coal use was estimated for the mean lifetime cumulative exposure to smoky coal, based on the distribution in the controls. In addition, smoky coal use was modeled as a linear relationship between the total amount of smoky coal use and the log odds of lung cancer. The linear relationship was checked by adding a quadratic term to the regression model and there was no significant improvement in fit. Furthermore, nonparametric logistic regression models using generalized additive models (14) also indicated that a linear model was appropriate for these data.

Additional variables used in the analysis were pack-years of tobacco smoking (defined as cigarette packs smoked daily multiplied by years of smoking, gram equivalents of leaf tobacco, assuming 1 g per cigarette), COPD, and a family history of lung cancer. The first three variables were defined using two levels according to the approximate mean of the distribution in the control group. COPD includes chronic bronchitis and/or emphysema. History of COPD was based on the county or communal hospital record. Chronic bronchitis was defined as having a medical history of cough and sputum on most days for at least 3 months over 2 consecutive years. Emphysema diagnosis was based on clinical symptoms, X-ray, and/or other hospital records. The subject was defined as having a positive family history of lung cancer if there was at least one case of lung cancer among first or second-degree relatives. In this study, most of the subjects with a positive family history had at least one first-degree relative who had developed lung cancer; only one subject had a second-degree family relative with a history of lung cancer. An ever-smoker was defined as a smoker of at least one cigarette per day for 6 months or longer. The association between smoky coal and lung cancer was stratified by *GSTM1* genotype, and tests were performed to assess departure from multiplicative effects. The analyses were also conducted both including and excluding the 17 cases who lacked tissue or cytological confirmation who had died within a year, and the results were very similar. The results presented here include these 17 cases.

Results

Table 1 shows the distribution of characteristics for both cases and controls. Age, sex, and type of fuel source were comparable. Eighty-eight % of the males were tobacco smokers, whereas only one female smoked. Therefore, the effect of tobacco smoking was evaluated only in male smokers. Ethnic group, educational level, household income, and dwelling type were comparable in cases and controls (not shown).

Table 2 shows association between several risk factors and the development of lung cancer in both unadjusted and adjusted analyses. A significant increase in the risk of lung cancer was found for the *GSTM1*-null genotype (OR, 2.3; 95% CI, 1.3–4.2). Compared to subjects who used less than 130 tons of smoky coal during their lifetime, heavier users had a 2.4-fold

Table 1 Distribution of subject characteristics in lung cancer patients and controls

Variables	Cases (n = 122) n (%)	Controls (n = 122) n (%)	P[a]
Categorical			
Sex			
Male	79 (64.8)	79 (64.8)	
Female	43 (35.2)	43 (35.2)	
Fuel Type			
Smoky coal	120 (98.4)	120 (98.4)	
Smokeless coal	2 (1.6)	2 (1.6)	
Ever Smoker (male)			
No	9 (11.4)	10 (12.7)	
Yes	70 (88.6)	69 (87.3)	0.81
Continuous[b]			
Age	55, 11	55, 12	0.46
Smoky coal use without ventilation (tons)	172.0, 105.6	130.3, 77.1	0.001
Pack-years (male)	27.6, 20.1	25.8, 22.3	0.65

[a] P based on χ^2 test or t test.
[b] Mean, SD.

Table 2 ORs and 95% CIs for lung cancer according to different factors

Factors	Cases n (%)	Controls n (%)	OR[a] (95% CI)	OR[b] (95% CI)
GSTM1				
GSTM1-positive	40 (32.8)	62 (49.2)	1.0	
Null	82 (67.2)	60 (50.8)	2.2 (1.3–3.7)	2.3 (1.3–4.2)
GSTT1				
GSTT1-positive	49 (40.2)	58 (47.5)	1.0	
Null	73 (59.8)	64 (52.5)	1.3 (0.8–2.2)	1.3 (0.7–2.3)
Smoky coal use without ventilation (tons)				
<130	51 (41.8)	72 (59.0)	1.0	
≥130	71 (58.2)	50 (41.0)	2.4 (1.3–4.4)	2.4 (1.3–4.4)
Pack-years (PY)[c]				
$0 < PY < 25$	27 (38.6)	36 (52.2)	1.0	
$PY \geq 25$	43 (61.4)	33 (47.8)	1.7 (0.9–3.1)	1.5 (0.8–2.9)
COPD				
No	76 (62.3)	87 (71.3)	1.0	
Yes	46 (37.7)	35 (28.7)	1.5 (0.9–2.5)	1.3 (0.7–2.2)
Family history of lung cancer				
No	102 (83.6)	108 (88.5)	1.0	
Yes	20 (16.4)	14 (11.5)	1.6 (0.7–3.5)	1.6 (0.6–3.8)

[a] ORs and 95%s CIs obtained by univariate conditional logistic regression analysis.
[b] ORs and 95% CIs adjusted for total smoky coal use without ventilation, pack-years, COPD, and family history of lung cancer by multiple conditional logistic regression.
[c] Evaluated only in male smokers by unconditional logistic regression.

(95% CI, 1.3–4.4) increased risk of lung cancer. Smoking more than 25 pack-years was associated with a 1.5-fold (95% CI, 0.8–2.9) increased risk of lung cancer.

Compared to subjects exposed to low levels of smoky coal (<130 tons) who were *GSTM1*-positive, the OR was 1.8 (95% CI, 0.8–4.1) for *GSTM1*-null subjects exposed to low levels of smoky coal (<130 tons) and 1.8 (95% CI, 0.7–4.6) for the *GSTM1*-positive subjects exposed to high levels of smoky coal (≥130 tons; Table 3). The OR for the joint effect of high levels of smoky coal exposure and the *GSTM1*-null genotype was 5.2 (95% CI, 2.1–12.6), although the test for multiplicative interaction was not significant ($P = 0.4$).

We also explored the association between smoky coal exposure as a continuous variable, which was consistent with a log-linear increase in lung cancer risk, and its potential interaction with *GSTM1* genotype. When coal use was expressed as a continuous variable, the risk of lung cancer was increased by 1.7-fold per 100 tons (95% CI, 1.3–2.4) for all subjects, by 1.2-fold per 100 tons (95% CI, 0.8–1.9) among *GSTM1*-positive subjects, and by 2.4-fold per 100 tons (95% CI, 1.6–3.9) among *GSTM1*-null genotype subjects (test for multiplicative interaction, $P = 0.05$). Results were negligibly affected after conducting sensitivity analysis by excluding subjects at the high extreme of smoky coal use.

Table 3 ORs[a] and 95% CIs for lung cancer in relation to *GSTM1* genotypes and smoky coal use

Total smoky coal use without ventilation (tons)	*GSTM1* Positive	*GSTM1* Null
<130	1.0 (reference)	1.8 (0.8–4.1)
	17/32	34/40
≥130	1.8 (0.7–4.6)	5.2 (2.1–12.6)
	23/30	48/20

[a] ORs and 95% CIs adjusted for pack-years, COPD, and family history of lung cancer by multiple logistic regression.

Discussion

We carried out a population-based case-control study of lung cancer in Xuan Wei County, China, and found that high levels of smoky coal use and the *GSTM1*-null genotype were each associated with increased risk. Furthermore, there was some evidence that the smoky coal-lung cancer association was stronger among subjects who were *GSTM1* null compared to individuals with a positive *GSTM1* genotype. These findings are consistent with our previous report that PAHs are probably the major class of lung carcinogens present in smoky coal (1) and with the well-established role of GSTM1 in the detoxification of these compounds (9).

Our study has several strengths. It was population based and had very high participation rates among both cases and controls. Furthermore, we were able to quantitatively estimate smoky coal use for each subject. In addition, genotyping was carried out twice on all samples to minimize genotype misclassification. Fifty-one % of our controls carried the *GSTM1*-null genotype, and 52.5% had the *GSTT1*-null genotype; these figures are in agreement with previous reports of the prevalence of these genotypes in Chinese populations (15–19). Finally, our series of lung cancer cases is relatively unique in that smoky coal exposure is the primary etiological factor, in contrast to tobacco for most populations. This is particularly so for nonsmoking women in Xuan Wei, whose lung cancer incidence rate is the highest in China (1).

Our study had a number of limitations. There is resistance in rural China to invasive medical procedures, such as biopsy, surgery, and autopsy. Only 105 (86%) of our cases were confirmed by histology or cytology. For the other 14% (n = 17 cases), we had to rely on chest X-ray, medical history and death within one year after diagnosis. However, restriction of the analysis to the 105 cases confirmed by examination of cytology or biopsy samples produced results that were similar to the analyses using the total study group. Second, our sample size was relatively small, and as such, our study had low power to detect both the crude main effects of genetic variants and interactions between genetic and environmental risk factors. Nevertheless, we did find some evidence that cumulative smoky coal use, when analyzed as a continuous variable, was more strongly associated with risk of lung cancer among subjects with the *GSTM1*-null genotype.

To our knowledge, there are no previous reports of *GSTM1* genotype and lung cancer risk within a population in which lung cancer risk is caused primarily by environmental PAH exposure. A recently reported cross-sectional study of coke oven workers, who are exposed to high levels of PAHs, found that individuals with the *GSTM1*-null genotype had elevated PAH-DNA adduct levels in peripheral blood lymphocytes (20). This provides some biological support for our observation that the *GSTM1*-null genotype increases lung cancer risk in the presence of substantial environmental PAH exposure.

A recent meta-analysis of *GSTM1* genotype and lung cancer risk reported that the *GSTM1*-null genotype was only weakly associated with lung cancer risk in the general population (21). However, the vast majority of lung cancer cases in these studies were most likely attributable to tobacco smoke, and there is still uncertainty about which of the many carcinogens in tobacco smoke are most important for lung cancer risk. In contrast, many of the lung cancer cases in our series were probably caused by exposure to PAHs. As such, they may represent a relatively unique population in which to study genetic modification of these compounds.

We found no association between the *GSTT1*-null genotype and lung cancer. This result could be attributable to the fact that GSTT1 is not important, or at least not rate-limiting, in the metabolism of PAHs (22). Alternatively, given our relatively small sample size, our null finding could represent a type II error.

In conclusion, we found that smoky coal use and the *GSTM1*-null genotype were associated with increased risk of lung cancer in Xuan Wei County. Furthermore, there was some evidence that the association between smoky coal and lung cancer was stronger among subjects with the *GSTM1*-null genotype. This study provides the first evidence, to our knowledge, that the *GSTM1*-null genotype may be associated with lung cancer risk attributable to environmental PAH exposure. This hypothesis should be evaluated in larger studies carried out within Xuan Wei County and other populations with substantial environmental exposure to PAHs.

Acknowledgments

We are grateful to Dongyun Yang, to Chaofu Huang for his assistance in our Xuan Wei data collection, and to Jeff Inmon at the United States Environmental Protection Agency for technical assistance with DNA isolation. We thank Dr. Montserrat Garcia-Closas at the National Cancer Institute for carrying out the nonparametric analysis of the data. We also thank Drs. Andy Olshan and Charles Poole at the University of North Carolina, Drs. Jay Lubin and Aaron Blair at the National Cancer Institute, Dr. Douglas Bell at National Institute of Environmental Health Sciences, and Drs. Robert Chapman and Jane Gallagher at the United States Environmental Protection Agency for reviewing the paper.

References

1. Mumford, J. L., He, X. Z., Chapman, R. S., Cao, S. R., Harris, D. B., Li, X. M., Xian, Y. L., Jiang, W. Z., Xu, C. W., Chuang, J. C., Wilson, W. E., and Cooke, M. Lung cancer and indoor air pollution in Xuan Wei, China. Science (Washington DC), *235:* 217–220, 1987.

2. Chapman, R. S., Mumford, J. L., Harris, D. B., He, Z. Z., Jiang, W. Z., and Yang, R. D. The epidemiology of lung cancer in Xuan Wei, China: current progress, issues, and research strategies. Arch. Environ. Health, *43:* 180–185, 1988.

3. He, X. Z., Chen, W., Liu, Z. Y., and Chapman, R. S. An epidemiological study of lung cancer in Xuan Wei County, China: current progress. Case-control study on lung cancer and cooking fuel. Environ. Health Perspect., *94:* 9–13, 1991.

4. Lan, Q., Chen, W., Chen, H., and He, X. Z. Risk factors for lung cancer in non-smokers in Xuanwei County of China. Biomed. Environ. Sci., *6:* 112–118, 1993.

5. Liang, C. K., Quan, N. Y., Cao, S. R., He, X. Z., and Ma, F. Natural inhalation exposure to coal smoke and wood smoke induces lung cancer in mice and rats. Biomed. Environ. Sci., *1:* 42–50, 1988.

6. Mumford, J. L., Helmes, C. T., Lee, X. M., Seidenberg, J., and Nesnow, S. Mouse skin tumorigenicity studies of indoor coal and wood combustion emissions from homes of residents in Xuan Wei, China with high lung cancer mortality. Carcinogenesis (Lond.), *11:* 397–403, 1990.

7. Seidegard, J., Vorachek, W. R., Pero, R. W., and Pearson, W. R. Hereditary differences in the expression of the human glutathione transferase active on trans-stilbene oxide are due to a gene deletion. Proc. Natl. Acad. Sci. USA, *85:* 7293–7297, 1988.

8. Ketterer, B., Harris, J. M., Talaska, G., Meyer, D. J., Pemble, S. E., Taylor, J. B., Lang, N. P., and Kadlubar, F. F. The human glutathione *S*-transferase supergene family, its polymorphism, and its effects on susceptibility to lung cancer. Environ. Health Perspect., *98:* 87–94, 1992.

9. Hayes, J. D., and Pulford, D. J. The glutathione *S*-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. Crit. Rev. Biochem. Mol. Biol., *30:* 445–600, 1995.

10. Hu, F., Wu, Y., Zhu, H., Guo, C., and Zhao, H. Natural survival of lung cancer observed in general in Xuan Wei county (in Chinese). Cancer, *8:* 42–43, 1989.

11. Scherczinger, C. A., Bourke, M. T., Ladd, C., and Lee, H. C. DNA extraction from liquid blood using QIAamp. J. Forensic. Sci., *42:* 893–896, 1997.

12. Bell, D. A., Taylor, J. A., Paulson, D. F., Robertson, C. N., Mohler, J. L., and Lucier, G. W. Genetic risk and carcinogen exposure: a common inherited defect of the carcinogen-metabolism gene glutathione *S*-transferase M1 (*GSTM1*) that increases susceptibility to bladder cancer. J. Natl. Cancer Inst., *85:* 1159–1164, 1993.

13. Chen, C. L., Liu, Q., and Relling, M. V. Simultaneous characterization of glutathione *S*-transferase M1 and T1 polymorphisms by polymerase chain reaction in American whites and blacks. Pharmacogenetics, *6:* 187–191, 1996.

14. Hastie, T., and Tibshirani, R. Generalized additive models. London: Chapman & Hall, 1990.

15. Seow, A., Shi, C. Y., Chung, F. L., Jiao, D., Hankin, J. H., Lee, H. P., Coetzee, G. A., and Yu, M. C. Urinary total isothiocyanate (ITC) in a population-based sample of middle-aged and older Chinese in Singapore: relationship with dietary total ITC and glutathione *S*-transferase M1/T1/P1 genotypes. Cancer Epidemiol. Biomark. Prev., *9:* 775–781, 1998.

16. Yu, M. C., Ross, R. K., Chan, K. K., Henderson, B. E., Skipper, P. L., Tannenbaum, S. R., and Coetzee, G. A. Glutathione *S*-transferase M1 genotype affects aminobiphenyl-hemoglobin adduct levels in white, black and Asian smokers and nonsmokers. Cancer Epidemiol. Biomark. Prev., *8:* 861–4, 1995.

17. Rothman, N., Hayes, R. B., Zenser, T. V., DeMarini, D. M., Bi, W., Hirvonen, A., Talaska, G., Bhatnagar, V. K., Caporaso, N. E., Brooks, L. R., Lakshmi, V. M., Feng, P., Kashyap, S. K., You, X., Eischen, B. T., Kashyap, R., Shelton, M. L., Hsu, F. F., Jaeger, M., Parikh, D. J., Davis, B. B., Yin, S., and Bell, D. A. The glutathione *S*-transferase M1 (*GSTM1*) null genotype and benzidine-associated bladder cancer, urine mutagenicity, and exfoliated urothelial cell DNA adducts. Cancer Epidemiol. Biomark. Prev., *5:* 979–983, 1996.

18. Setiawan, V. W., Zhang, Z. F., Yu, G. P., Li, Y. L., Lu, M. L., Tsai, C. J., Cordova, D., Wang, M. R., Guo, C. H., Yu, S. Z., and Kurtz, R. C. *GSTT1* and *GSTM1* null genotypes and the risk of gastric cancer: a case-control study in a Chinese population. Cancer Epidemiol. Biomark. Prev., *9:* 73–80, 2000.

19. Gao, Y., and Zhang, Q. Polymorphisms of the *GSTM1* and *CYP2D6* genes associated with susceptibility to lung cancer in Chinese. Mutat. Res., *444:* 441–449, 2000.

20. Brescia, G., Celotti, L., Clonfero, E., Neumann, G. H., Forni, A., Foa, V., Pisoni, M., Ferri, G. M., and Assennato, G. The influence of cytochrome P450 1A1 and glutathione *S*-transferase M1 genotypes on biomarker levels in coke-oven workers. Arch. Toxicol. *73:* 431–439, 1999.

21. Houlston, R. S. Glutathione *S*-transferase M1 status and lung cancer risk: a meta-analysis. Cancer Epidemiol. Biomark. Prev., *8:* 675–682, 1999.

22. Rebbeck, T. R. Molecular epidemiology of the human glutathione *S*-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility. Cancer Epidemiol. Biomark. Prev., *6:* 733–743, 1997.